Remarks

The claims are directed to methods for inhibiting pregnancy or decreasing production of steroids in a mammal comprising administering a compound inhibiting uptake, binding or transport of cholesteryl ester by SR-BI in the mammal in an amount effective to to inhibit pregnancy or to decrease production of steroids in disorders involving steroidal overproduction. (see page 7, line 19- page 8, lines 5; page 13; lines 19-20, paragraph bridging pages 10 and 11; and lines 15-20, bridging pages 12 and 13). The compound may be selected to alter expression of SR-BI (decreased or increased) in a tissue (see page 10, lines 19-27). The compound may alter (increases or decreases) the binding of SR-BI to high density lipoprotein including cholesteryl ester or other lipoproteins (page 12, lines 16-18; Example 2). The disorder may be treated by decreasing the production of steroids, differentially altering the activity of, or expression of, SR-BI in different tissues, increasing SR-BI expression in reproductive tissues (while decreasing, or not increasing, SR-BI expression in the liver) (page 12, lines 25-26; page 13, lines 14-15; page 13, lines 23-25; and lines 19-2, bridging pages 10-11). The compound may be an antibody to SR-BI (page 12, lines 24-28), or a drug that decreases production of steroids *via* selective binding to SR-BI (page 11, lines 10-17). The compound may decrease cholesterol levels to decrease steroid levels (page 12, lines 26-28).

Applicant is the first to recognize that lipoprotein and/or cholesterol levels affects a female's ability to reproduce. Applicant is the first to recognize that SR-BI, by virtue of its role as the only known transporter of cholesterol, which is critical to steroid production, plays a major role in female reproduction. Applicant demonstrated the criticality of SR-BI, and its role on

lipoprotein and cholesterol levels, using SR-BI knockout mice. The homozygous knockout females are unable to carry a fetus to term. Heterozygotes are able to do so. These studies are described in the patent application as filed. Applicant has subsequently shown that treatment of the mice with a known cholesterol lowering drug such as probucal, which normalizes the cholesterol values and the lipoprotein levels, to a degree, restores fertility to these animals.

The data presented in the specification clearly demonstrate that multiple compounds have been identified and are representative of widely disparate species, ranging from nucleic acid molecules encoding SR-BI to organic compounds for lowering cholesterol.

In example 5, applicant demonstrated that transient increases in SR-BI expression following administration of an adenoviral vector encoding SR-BI results in a decrease in cholesterol levels. In example 6, the applicant demonstrated that SR-BI knockout animals exhibit the opposite phenotype; increased cholesterol levels (see Table 3). Data in example 7 further shows that these animals are also infertile. Antibody blocking studies have also showed similar results using antibodies to block cholesterol transport, resulting in lowered cholesterol levels, as described in Example 8, page 55.

The reagents and methods provided in the present specification were used to subsequently show the restoration of fertility in an SR-BI knockout mouse (or their transplanted oocytes) in the absence of ovarian and/or extraovarian SR-BI expression by manipulations that modify the structure, composition and/or abundance of their abnormal plasma lipoproteins. These manipulations centered around the administration of probucal, a cholesterol lowering drug

(see the response mailed on February 15, 2002; copy of Meittinen, *et al.*, *J. Clin. Invest.* 108:1717-1722 (2001)).

The application therefore teaches one skilled in the art that SR-BI is essential for normal female fertility; that decreasing levels of SR-BI activity decreases cholesterol levels and alters lipoprotein levels; and that restoring SR-BI activity normalized cholesterol levels and lipoprotein profiles, with a concurrent increase in steroidogenesis and female fertility. The application further teaches that one can use any number of compounds to alter SR-BI levels: viral vectors to increase SR-BI expression; antibodies to block SR-BI activity and concurrent transport of cholesterol; and organic molecules identified by routine screening assays using SR-BI binding and uptake studies. These compounds alter SR-BI activity either by increasing the amount of transport or by decreasing transport (for example, using viral vectors or antibodies). These clearly and unequivocally affect female fertility as claimed.

The present application, and its analysis of SR-BI knockout mice, ties together fertility and cholesterol level. The direct correlation that exists between cholesterol/HDL and the existence of SR-BI, lies at the core of the claimed method. Many compounds that already exist for regulating cholesterol levels can be used to inhibit fertility *via*, the inhibition of SR-BI expression or activity. It would not require undue experimentation to identify these compounds, the patients to be treated, or what constitutes an effective amount. Moreover, one skilled in the art would have no difficulty in identifying the scope of the claimed method in view of the specification, the examples, and the knowledge available to those skilled in the art.

For the foregoing reasons, Applicant submits that the amended claims are patentable.

Respectfully submitted,

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